FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **112701-335**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): **10/070486**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08731	**7 September 2000**	**13 September 1999**

TITLE OF INVENTION: **HIGH LIPID DIET**

APPLICANT(S) FOR DO/EO/US: **Turini et al.**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☒ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Return Receipt Postcard
Express Mail Label No.: EL 727 382 483 US

JC13 Rec'd PCT/PTC 06 MAR 2002

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/070486	PCT/EP00/08731	112701-335

24. The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	40 - 20 =	20	x $18.00	**$360.00**
Independent claims	6 - 3 =	3	x $84.00	**$252.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**

TOTAL OF ABOVE CALCULATIONS =	**$1,502.00**
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.	**$0.00**
SUBTOTAL =	**$1,502.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +	**$0.00**
TOTAL NATIONAL FEE =	**$1,502.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐	**$0.00**
TOTAL FEES ENCLOSED =	**$1,502.00**
	Amount to be: refunded $
	charged $

a. ☒ A check in the amount of **$1,502.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **02-1818** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Robert M. Barrett, Esq.
ATTORNEYS FOR APPLICANTS
Bell, Boyd & Lloyd LLC
P.O. Box 1135
Chicago, Illinois 60690-1135

SIGNATURE

Robert M. Barrett
NAME

30,142
REGISTRATION NUMBER

March 6, 2002
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Turini et al.
Appl. No.: PCT/EP00/08731
Filed: Filed Herewith
Title: HIGH LIPID DIET
Art Unit: Unknown
Examiner: Unknown
Docket No.: 112701-335

Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified patent application as follows:

In the Specification:

On page 1, line 1, delete "High Lipid Diet" and substitute the following:

--SPECIFICATION

TITLE OF THE INVENTION

"HIGH LIPID DIET"--

On page 1, at line 37, insert the following:

--SUMMARY OF THE INVENTION--

On page 6, line 22, please delete "specific embodiments of the invention will now be described in detail with reference to the accompanying drawings in which" and substitute therefor --Additional features and advantages of the present invention are described in and will be apparent from the Detailed Description of the Presently Preferred Embodiments and the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS--

On page 7, line 13, please insert:

--DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved compositions as well as methods of treatment. More specifically, the composition of the present invention and treatment can be used for the treatment or prevention of sepsis or inflammatory shock. The composition of the present invention includes greater than 35% of its caloric content as a lipid.

By way of example and not limitation, examples of the present invention will now be set forth.--

In the Claims:

Please amend Claims 1-8 as follows:

1. A method of treating sepsis comprising the steps of administering to a patient with sepsis a therapeutically effective amount of a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

2. A method of reducing the risk of sepsis comprising the steps of administering to a patient at risk of sepsis comprises a therapeutically effective amount of a composition, which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

3. A method of producing a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition, comprising the steps of blending constituents including at least one lipid, liquefying a blended mixture and homogenising the liquefied blended mixture to produce a product wherein greater than 35% of the total energy of the composition is provided by lipid.

4. A composition comprising at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition, about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

5. A composition according to claim 4, which comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

6. A composition according to claim 4, which comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

7. A composition according to claim 4, which comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

8. A composition according to claim 4 for enteral administration which includes at least one component selected from the group consisting of an acceptable carrier, diluent and adjuvant.

Please add newly-submitted Claims 9-40 as follows:

9. The method of claim 1 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

10. A method of treating inflammatory shock comprising the step of administering to a patient suffering inflammatory shock a therapeutically effective amount of a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

11. The method of claim 1 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

12. The method of claim 1 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

13. The method of claim 1 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

14. The method of claim 1 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

15. The method of claim 1 wherein the composition is administered enterally.

16. A method for reducing the risk of inflammatory shock comprising the step of administering to a patient at risk of inflammatory shock a therapeutically effective amount of a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

17. The method of claim 2 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

18. The method of claim 2 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

19. The method of claim 2 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

20. The method of claim 2 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

21. The method of claim 2 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

22. The method of claim 2 wherein the composition is administered enterally.

23. The method of claim 3 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

24. The method of claim 3 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

25. The method of claim 3 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

26. The method of claim 3 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

27. The method of claim 3 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

28. The method of claim 3 wherein the composition is administered enterally.

29. The method of claim 10 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

30. The method of claim 10 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

31. The method of claim 10 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

32. The method of claim 10 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

33. The method of claim 10 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

34. The method of claim 10 wherein the composition is administered enterally.

35. The method of claim 16 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

36. The method of claim 16 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

37. The method of claim 16 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

38. The method of claim 16 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

39. The method of claim 16 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

40. The method of claim 16 wherein the composition is administered enterally.

REMARKS

Pursuant to this Preliminary Amendment, Claims 1-8 have been amended and newly-submitted Claims 9-40 have been added. Additionally, minor amendments have been made to the specification.

The Preliminary Amendment does not add new matter. Moreover, Applicants note for the record, the Preliminary Amendment is not being used for purposes of narrowing the claims to avoid prior art. Rather, the Preliminary Amendment is being made to place the claims in proper U.S. format as well as add additional claims. Therefore, Applicants do not intend to disclaim any subject matter in view of this Preliminary Amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Versions with Markings to Show Changes Made.**"

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____

Robert M. Barrett
Reg. No. 30,142
P.O. Box 1135
Chicago, Illinois 60690-1135
Phone: (312) 807-4204

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On page 1, line 1, delete "High Lipid Diet" and substitute the following:

--SPECIFICATION

TITLE OF THE INVENTION

"HIGH LIPID DIET"--

On page 1, at line 37, insert the following:

--SUMMARY OF THE INVENTION--

On page 6, line 22, please delete "specific embodiments of the invention will now be described in detail with reference to the accompanying drawings in which" and substitute therefor --Additional features and advantages of the present invention are described in and will be apparent from the Detailed Description of the Presently Preferred Embodiments and the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS--

On page 7, line 13, please insert:

--DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved compositions as well as methods of treatment. More specifically, the composition of the present invention and treatment can be used for the treatment or prevention of sepsis or inflammatory shock.

By way of example and not limitation, examples of the present invention will now be set forth.--

In the Claims:

Please amend Claims 1-8 as follows:

1. (Amended) [Use] A method of treating sepsis comprising the steps of administering to a patient with sepsis a therapeutically effective amount of a composition[,] which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy

of the composition [for use in the manufacture of a medicament, functional food or nutritive product for the treatment or prevention of sepsis or inflammatory shock].

2. (Amended) A method of [treatment or prevention of] reducing the risk of sepsis [or inflammatory shock which] comprising the steps of administering to a patient at risk of sepsis comprises [administering an] a therapeutically effective amount of a composition, which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

3. (Amended) A method of producing a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition, [having] comprising the steps of blending [the] constituents including at least one lipid, liquefying [the] a blended mixture and homogenising the liquefied blended mixture to produce a product wherein greater than 35% of the total energy of the composition is provided by lipid.

4. (Amended) A composition [for use as a medicament, functional food or nutritive product, which comprises] comprising at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition, [which further comprises] about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

5. (Amended) A composition according to claim 4, which comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

6. (Amended) A composition according to claim 4 [or 5], which comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA [or] and DHA.

7. (Amended) A composition according to [any of] claim 4 [to 6], which comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) [or] and arachidonic acid (20:4, n-6).

8. (Amended) A composition according to [any of] claim 4 [to 7] for enteral administration which [comprises] includes at least one component selected from the group consisting of an acceptable carrier, diluent [or] and adjuvant.

Please add newly-submitted Claims 9-40 as follows:

9. The method of claim 1 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

10. A method of treating inflammatory shock comprising the step of administering to a patient suffering inflammatory shock a therapeutically effective amount of a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

11. The method of claim 1 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

12. The method of claim 1 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

13. The method of claim 1 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

14. The method of claim 1 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

15. The method of claim 1 wherein the composition is administered enterally.

16. A method for reducing the risk of inflammatory shock comprising the step of administering to a patient at risk of inflammatory shock a therapeutically effective amount of a composition which comprises at least one lipid wherein the lipid provides greater than 35% of the total energy of the composition.

17. The method of claim 2 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

18. The method of claim 2 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

19. The method of claim 2 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

20. The method of claim 2 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

21. The method of claim 2 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

22. The method of claim 2 wherein the composition is administered enterally.

23. The method of claim 3 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

24. The method of claim 3 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

25. The method of claim 3 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

26. The method of claim 3 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

27. The method of claim 3 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

28. The method of claim 3 wherein the composition is administered enterally.

29. The method of claim 10 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

30. The method of claim 10 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

31. The method of claim 10 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

32. The method of claim 10 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

33. The method of claim 10 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

34. The method of claim 10 wherein the composition is administered enterally.

35. The method of claim 16 wherein the composition is in a form selected from the group consisting of medicament, functional food and nutritive product.

36. The method of claim 16 wherein the composition comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

37. The method of claim 16 wherein the composition comprises a n-6/n-3 fatty acid ratio of about 2/1 to about 7/1.

38. The method of claim 16 wherein the composition comprises at least one n-3 fatty acid selected from the group consisting of α-linolenic acid, EPA, DPA and DHA.

39. The method of claim 16 wherein the composition comprises at least one n-6 fatty acid selected from the group consisting of linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleninic acid (18:4, n-6) and arachidonic acid (20:4, n-6).

40. The method of claim 16 wherein the composition is administered enterally.

13/pats

High Lipid Diet

The present invention relates to a composition for use as a medicament, functional food or nutrative product which comprises a high lipid content, a method of preparing the composition; use of the composition in the manufacture of a medicament, functional food or nutritional product; and a method of treatment or prevention of sepsis or inflammatory shock which comprises administering an effective amount of the composition.

Within the context of this specification the word "comprises" is taken to mean "includes, among other things". It is not intended to be construed as "consists of only".

The abbreviation EPA represents eicosapentaenoic acid (20:5,n-3); DPA represents docosapentaenoic acid (22:5,n-3); DHA represents docosahexaenoic acid (22:6,n-3); MCT represents medium chain triglycerides and LC-PUFA represents long chain polyunsaturated fatty acid.

It is generally recommended that a diet contains a lipid content which provides about 30% total energy of the diet for a normal healthy individual.

Conventional diets are generally high in saturated fat and have a high ratio of n-6/n-3 fatty acids. A problem with consuming this type of diet is that saturated fat is implicated in cardiovascular disease and cancer. In addition, a high ratio of n-6/n-3 fatty acids is implicated in inflammatory disorders. Furthermore, it is well known that patients having chronic intestinal inflammation are at risk of developing certain types of cancer.

The quantity and quality of lipids for critically ill patients at risk of developing infectious and septic complications is a matter of debate. It has now been found that the quantity of lipids is important for clinical outcome, in particular for limiting body weight and muscle mass losses as well as for normalising the levels of proteins produced in the acute phase of septic shock. This provides support for maintaining a high lipid content in enteral products destined for critically ill patients.

Remarkably, it has now been found that a composition which comprises a high lipid content has good effects on recovery or prevention of sepsis or inflammatory shock. This is unexpected because lipids in the diet are thought to be not well metabolised during sepsis or inflammatory shock since it is well known that sepsis induces hypertriglyceridemia.

Furthermore, it has now been found that compositions having specific fatty acid profiles have particularly good effects.

Suprisingly, results now obtained show:

Enteral diets with a high lipid content have beneficial effect on the recovery from an acute inflammatory stress (acute phase protein concentration) but also on clinical parameters (body weight loss and nitrogen excretion).

The beneficial effect of a high lipid diet is observed when lipid level is increased after the induction of stress (curative effect) but is also pronounced when a high lipid diet is given from one week before the stress.

Accordingly, in a first aspect the invention provides a composition for use as a medicament, functional food or nutrative product which comprises at least one lipid wherein the lipid provides greater than 35% total energy of the composition.

In a second aspect, the invention provides a method of producing a composition according to the invention having the steps of blending the constituents, liquefying the blended mixture and homogenising.

In a third aspect the invention provides the use of a composition which comprises a lipid content that provides greater than 35% total energy of the composition in the manufacture of a medicament, functional food or nutritive product for the treatment or prevention of sepsis or inflammatory shock.

In a forth aspect the invention provides a method of treatment or prevention of sepsis or inflammatory shock which comprises administering an effective amount of a composition which comprises a lipid content which provides greater than 35% total energy of the composition.

Preferably a composition according to an embodiment of the invention comprises lipid wherein the lipid content provides a lower limit of about 40%, more preferably about 50% and/or an upper limit of about 75%, more preferably about 60% total energy of the composition.

Preferably a composition according to an embodiment of the invention comprises a composition which comprises MCT (medium chain triglycerides). More preferably a composition according to an embodiment of the invention comprises about 25% to about 70% MCT by weight of total lipid. Even more preferably a composition according to an embodiment of the invention comprises about 40% to about 60% MCT by weight of total lipid.

More preferably a composition according to an embodiment of the invention comprises low levels of saturated fatty acids excluding MCT. Preferably the composition comprises less than about 15% by weight saturated fatty acids excluding MCT.

Preferably, an embodiment of a composition according to the invention comprises a low n-6/n-3 fatty acid ratio. More preferably the ratio is about 2/1 to 7/1, even more preferably the ratio is about 2/1 to 5/1.

Preferably, an embodiment of a composition according to the invention comprises about 3% to about 5% of total lipids of at least one n-3 fatty acid selected from α-linolenic acid, EPA, DPA,or DHA derived from any source. More preferably a composition according to an embodiment of the invention comprises α-linolenic acid.

Preferably, an embodiment of a composition according to the invention comprises at least one n-6 fatty acid. Preferably it is selected from linoleic acid (18:2, n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleinic acid (18:4, n-6) or arachidonic acid (20:4, n-6). More preferably, it is selected from the group which comprises linoleic acid (18:2, n-6) and γ-linolenic acid (18:3, n-6). Most preferably it is linoleic acid (18:2, n-6).

Preferably the fatty acid or lipid source is selected from the group comprising natural oils, single cell oils, structured lipids and synthetic oils. Preferable sources of fats or lipids are olive oil, corn oil, sunflower oil, rapeseed oil, corn oil, hazelnut oil, safflower oil, canola oil, fish oil, milk fat, soya or the like. Fractionated coconut oils are a preferable source of medium chain triglycerides. A mixture of soybean oil, canola or olive oil, and MCT may be used.

Preferably a dose of about 0.5 to about 2.5 litres of the composition is provided per day. More preferably the dose is about 1.5 to 2 litres per day. Of course the exact dose would depend on the patient condition and status.

Preferably, a composition according to an embodiment of the invention is in a form suitable for enteral administration. Preferably it comprises an acceptable carrier, diluent or adjuvant.

Preferably an embodiment of the composition includes a protein source, a carbohydrate source and a lipid source.

Preferably, the protein source is a high quality protein source; for example milk protein, whey protein, casein protein, or soy protein, or mixtures of these

proteins. The protein source may be in the form of intact protein or may be hydrolysed. Other protein sources such as rice, pea and oat protein, or mixtures thereof, may also be used. Further, if desired, the protein source may include free amino acids.

Preferably the protein source provides about 10% to about 25% of the energy of the composition. For example, the protein source may provide about 12% to about 18% of the energy of the composition; preferably about 15% of the energy of the composition.

The carbohydrate source may be any suitable carbohydrate or carbohydrate mixture. For example, the carbohydrate source may be maltodextrin, modified starch, amylose starch, tapioca starch, corn starch, or fructose, or mixtures thereof. Maltodextrin is preferred if low osmolarity is required.

Preferably the carbohydrate source provides about 12% to about 55% of the energy of the composition; preferably about 25% to about 45% of the energy. For example, the carbohydrate source may provide about 40% of the energy of the composition.

Preferably an embodiment of the composition includes a complete vitamin and mineral profile. For example, sufficient vitamins and minerals may be provided to supply about 25% to about 250% of the recommended daily allowance of the vitamins and minerals per 1000 calories of the nutritional composition. In addition, the composition preferably has an osmolarity of about 200 mOsm/l to about 400 mOsm/l; for example about 250 mOsm/l to about 350 mOsm/l. Furthermore, the energy density of the composition is preferably about 700 kcal/l to about 1500 kcal/l; for example about 1000 kcal/l.

Preferably an embodiment of the composition is in the form of a ready-to-use formulation. In this form, the composition may be fed to a patient via a nasogastric tube, jejunum tube or by having the patient drink it. As such, the composition may be in a variety of forms; for example as a fruit juice-type beverage, a milk shake-type beverage or the like. In an alternative embodiment the composition is preferably in soluble powder form for reconstitution prior to use.

Preferably, an embodiment of the composition includes a flavour, sweetener or other additive. An artificial sweetener such as acetosulfame or an L-aspartyl based sweetener may be used; for example aspartame.

Preferably, an embodiment of the composition is produced according to a conventional method; for example, by blending together the protein source, a carbohydrate source, and a lipid source. Emulsifiers may be included in the blend. Vitamins and/or minerals may be added, but are usually added later to avoid thermal degradation. Lipophilic vitamins, emulsifiers or the like may be dissolved into the lipid source prior to blending. Water, preferably water which has been subjected to reverse osmosis, may be mixed in to form a liquid mixture. The temperature of the water is preferably about 50°C to about 80°C to aid dispersal of the ingredients. Commercially available liquefiers may be used to form the liquid mixture.

The liquid mixture may be thermally treated to reduce bacterial loads. For example, the liquid mixture may be rapidly heated to a temperature in the range of about 80°C to about 110°C for about 5 seconds to about 5 minutes. This may be carried out by steam injection or by heat exchanger; for example a plate heat exchanger.

Preferably the liquid mixture is cooled to about 60°C to about 85°C; for example by flash cooling. The liquid mixture may be homogenised; for example in two stages at about 7 MPa to about 40 MPa in the first stage and about 2 MPa to about 14 MPa in the second stage. The homogenised mixture may be further cooled to add any heat sensitive components; such as vitamins and minerals. The pH and/or solids content of the homogenised mixture is conveniently standardised.

To produce a liquid product, the homogenised mixture is preferably aseptically filled into suitable containers. Aseptic filling of the containers may be carried out by pre-heating the homogenised mixture (for example to about 75 to about 85°C) and injecting steam into the homogenised mixture to raise the temperature to about 140 to about 160°C; for example at about 150°C. The homogenised mixture may be cooled, for example by flash cooling, to a temperature of about 75 to about 85°C. The homogenised mixture may be further homogenised,

cooled to about room temperature and filled into containers. Suitable apparatus for carrying out aseptic filling of this nature is commercially available.

To produce a powder product, the homogenised mixture is preferably dried to powder; for example by spray drying. Preferably, conventional procedures are used.

Preferably, an embodiment of the composition in liquid form is administered by tube feeding, by gravity, or pump. In this form, the composition preferably has a viscosity of less than about 12 cp at room temperature.

Preferably an embodiment of the composition is suitable for clinical use, for example as a nutritional support for human or animal patients; particularly patients requiring long term nutritional support. Furthermore, the composition is preferably suitable for patients with normal digestive function.

It will be appreciated that the composition may be in a form other than that suitable for clinical nutrition. For example, the composition may be in the form of a dessert, cereal, yoghurt, snack bar, or the like. If fed to pets, the enteral composition may be in the form of dried kibble, meat emulsion, or formulated emulsion.

Specific embodiments of the invention will now be described in detail with reference to the accompanying drawings in which:

Figure 1 shows the results, in rats, of measurements of growth before infection.

Figure 2 shows results of food conversion efficiency which was 35% lower with a 35% lipid diet in rats than with a 15% lipid diet in rats.

Figure 3 shows the results of rat weight changes post-infection.

Figure 4 shows the results of cumulative nitrogen excretion in rat urine for 6 days after infection.

Figure 5 shows the results of experiments investigating the effect of a high lipid diet on rat spleen weight.

Figures 6 and 7, from two independent studies, show the results of effects on rat white blood cells.

Figures 8 and 9, from two independent studies, show the results of effects on rat orosomucoid plasma levels.

Figures 10 and 11, from two independent studies, show the results of effects on rat albumin plasma levels.

Figure 12 shows the results of effects of dietary lipid levels on rat triglyceride plasma levels.

Figure 13 shows results of rat body weight change post-infection; this figure is part of example 2.

Example 1

This example relates to the amount of lipid in the diet.

Remarkably it has now been found that there is a beneficial amount and profile of lipid in the diet, particularly in enteral products for critically ill patients. The effect of a high lipid diet in cases of acute stress has now been studied.

An animal model of sepsis in rats has now been used which permits testing of diets on the recovery from a condition representative of inflammatory syndromes observed in different clinical situations (see Breuille et al, Infection and Immunity, 67, 1079-1085, (1999)). It is important to note that the diets exemplified in rats must be correlated to diets for other mammals, for example humans. For example, a high lipid diet for a rat includes 35% of calories from lipids whereas a high lipid diet for a human includes at least about 35% to about 100% calories from lipids.

Two experiments, labeled Experiment 1 (Expt 1) and Experiment 2 (Expt 2) respectively, were carried out to assess the recovery of rats from sepsis when they were enterally fed with diets containing either 15% or 35% of calories as lipids. The second amount corresponds to more than twice the amount of lipid that rats usually have in their laboratory diet.

In the first experiment, rats received either a 15% or 35% lipid diet throughout the Experiment, i.e. 6 days prior to infection and 10 days post-infection.

In the second experiment, all rats received a 15% lipid diet during a preinfection period and were then randomly divided to continue either with a 15% diet post-infection or a high 35% lipid diet. Beneficial effects of the high lipid diet on different parameters were observed in response to infection: remarkably,

parameters measured returned to normal values faster with the high (35%) lipid diet compared to the low (15%) lipid diet.

In the first experiment the diets set out below were used:

High lipid diet (lipids at 35% of energy)

Parameter	Unit	Specification	Analysed
Energy	Kcal/100 ml	100	
Proteins	G/100 ml	3.75	
Lipids	G/100 ml	3.9	
Carbohydrates	G/100 ml	12.5	
Fatty acid pattern			
C14:0	% of total FA	Not fixed	0.3
C16:0	% of total FA	Not fixed	13
C18:0	% of total FA	Not fixed	6.4
C18:1 n-9	% of total FA	Not fixed	20
C18:2 n-6	% of total FA	Not fixed	54
C18:3 n-3	% of total FA	Not fixed	4.8

Low lipid diet (lipids at 15% of energy)

Parameter	Unit	Specification	Analysed
Energy	Kcal/100 ml	100	
Proteins	G/100 ml	3.75	
Lipids	G/100 ml	1.67	
Carbohydrates	G/100 ml	17.5	

The fatty acid composition of the low lipid diet was similar to the high lipid diet.

Diets were perfused continuously in the stomach. Four groups of animals were studied (n=11 in each group, at reception and inclusion of animals). (1)INF 15 group: infected animals . These rats received the 15% lipid diet (lipid = soybean oil) before and after infection. (2) PF 15 group: pair-fed animals of INF 15 (sham-infected with saline). These rats received the 15% lipid diet (lipid = soybean oil) before and after infection. (3) INF 35 group: infected animals . These rats received the 35% lipid diet (lipid = soybean oil) before and after

infection. (4) PF 35 group: pair-fed controls of INF 35 (sham-infection with saline). These rats received the 35% lipid diet (lipid = soybean oil) before and after infection.

All enteral products were isonitrogenous and isocaloric. They only differed in their relative content in lipids/carbohydrates. For technical reasons, proteins were provided in form of peptides since whole protein diets involved catheter obstruction issues.

To induce sepsis animals were infected by intravenous injection (via a tail vein) of 0.5ml of an E.coli suspension with a theoretic content of $1.0x10^9$ bacteria/ml.

After injection of bacteria or saline solution, enteral nutrition was progressively reintroduced..

In the second Experiment the same batches of diets as used in the first Experiment were used. Differences between the first Experiment and the second Experiment protocols were the following :

1) C (n=6) : control animals received the 15% lipid diet (lipid = soybean oil)
2) INF 15 : infected animals . These rats received the 15% lipid diet for the whole of the second Experiment.
3) PF 15 : pair-fed animals of INF 15 (sham-infection with saline).
4) INF 35 : infected animals . These rats received the 15% lipid diet before infection and the 35% lipid diet after infection in the second Experiment.
5) PF 35 : pair-fed controls of INF 35 (sham-infection with saline).
6) Rate of refeeding after infection was slightly higher than in the first Experiment (additional 10% on each day).

Body Weight before Infection:

The overall trend of the first Experiment can be visualized as a straight line (see figure 1). It is clear that the two groups start to show different weight gains after day 3: animals fed with the 15% lipid diet exhibited a better growth than with the 35% diet. This clearly confirms that in healthy rats, high lipid diets are not recommended and that for healthy rats 15% of total calories in the form of lipids provides a better diet than 35% of total calories in the form of lipids.

Body weight change after Infection :

Body weight changes were similar in both groups and in both experiments. Body weight loss paralleled the food intake curve. Therefore, after the initial body

weight loss, there was a progressive growth recovery as soon as food intake reached 50% of the ad libitum food intake.

The results show that the differences between INF 15% and INF 35% change after 6 days: before day 6 , the values for INF 35% are greater than INF 15%, but after day 6, there is a trend for a change. Therefore, there is a smaller body weight loss at the onset of infection that can be interpreted as a response of the organism to a high lipid diet. However no difference was observed in the second experiment, suggesting that the beneficial effect is more pronounced if the diet has been enriched with lipid before infection.

The results of the 2 experiments taken together lead to the important conclusion that a high lipid diet limits body weight loss. Furthermore, it is particularly effective if the diet has been enriched with lipid before infection.

Urinary nitrogen excretion :

It is interesting to observe nitrogen excretion at the same time as body weight changes since increased protein catabolism is known to be reflected in muscle atrophy and body weight loss. Indeed, increased proteolysis is generally associated with increased nitrogen excretion in urine.

Trends of urinary nitrogen excretion are in contrast when one looks at infected animals and their pair fed controls. After infection, INF rats (particularly those with 15% lipid diet) increase their urinary excretion until day 2, then level off their values (this is observed in both experiments). The opposite can be observed for both PF groups.

In the first Expt, there was a tendency for a smaller daily nitrogen excretion of INF35 compared to INF15. This trend was observed on each day. Pair-wise differences between infected and pair fed animals show that infected animals lost more nitrogen. This effect was more pronounced in the 15% formula than in the 35% one and differences between INF15 and INF35 were significant on days 2 and 3 after infection.

The same beneficial effect of the 35% formula was confirmed when urinary nitrogen was expressed as cumulative excretion from day 0 to day 6 postinfection ($p<0.05$), see fig 4.

In the second Experiment, the limitation of nitrogen loss was also observed with the high lipid diet on day 2 and 3 after infection ($p<0.05$).

The results lead to the conclusion that a high lipid diet has a beneficial effect for limitation of nitrogen loss induced by sepsis, suggesting a potential decrease of muscle proteolysis (which is dramatically increased in acute inflammatory conditions).

Tissue Weight:

High lipid diets have been shown to be beneficial for limitation of muscle atrophy and for return of spleen weight to a normal value.

White Blood Cell Counts:

High lipid diets have been shown to be beneficial for acceleration of normalisation of white blood cell counts.

Protein Concentrations In Plasma:

Proteins produced in the acute phase of sepsis exhibit changes in their concentration during inflammation. A high lipid content in the diet has been shown to accelerate the normalisation of accute phase protein concentration. This has been observed for positive and negative accute phase proteins.

Example 2

This example relates to the profile of lipids in the diet.

Whereas Example 1 shows the results and conclusions of providing a diet high in lipid content, Example 2 is directed to the the qualitative effects of dietary fatty acids on inflammatory parameters. The same rat model of sepsis and the same bacterial suspension was used.

The following table summarises the fatty acid composition of the diet formulations.

Table 6

	Diet A	Diet B	Diet C	Diet D	Diet E
Source	Soja Olive oil MCT	Soja Canola oil MCT	Olive oil Fish oil MCT	Olive oil Canola oil Safflower oil MCT	Soja Canola oil Milk fat
% Total FA (Weight%)					
MCT	38.5	38.5	38.5	38.5	5.1

SAT[1]	49.0	49.0	52.2	49.0	50.0
18:1n-9	36.8	27.3	27.3	27.3	27.3
n-6 PUFA	10.5	18.5	14.5	21.8	16.0
n-3 PUFA	2.3	4.1	3.2	1.0	3.6
n-6/n-3	4.5	4.5	4.5	21.8	4.5

[1]Includes MCT

Animals and Diets

Five groups (n=10 per group) of Sprague Dawley rats were studied. All animals received basic powder rat chow and water ad libitum for 4 days, prior to being randomly assigned to one of 5 diets (A-E in the table above) containing 15% fat as energy and differing only in their fatty acid composition. The rats were fed their dietary treatment ad libitum prior to (7 days) and post induction (10 days) of sepsis.

The diets were prepared according to the table above and as a powder.

Body weight change Before infection

Small differences in food intake and growth rate were detected by the bootstrap procedure of analyses with higher food intake and gain weight in groups B and C compared to the other groups. However, at day 0, no difference in average body weight was observed.

Body Weight Change After Infection

In all groups, animals exhibited an important body weight loss just after infection (Fig. 13). After that, body weight remained about stable (or tended to slightly decrease) until day 6 after infection. In all groups, we observed a recovery between days 6 and 10 postinfection.

The data strongly suggested beneficial effects of feeding animals diets containing high levels of MCT, in combination with α-linolenic acid (18:3,n-3) as the source of n-3 fatty acid (diets A and B), as compared to all other dietary treatments (C, D and E). The dietary fatty acid composition appeared to have an impact on body weight loss and on the recovery in response to infection.

Animals fed fish oil (Diet C) as a source of the n-3 long-chain polyunsaturated fatty acids, eicosapentaenoic acid (20:5,n-3, EPA) and docosahexaenoic acid (22:6,n-3, DHA), did not exhibit the similar beneficial response compared to animals fed α-linolenic acid (Diets A and B). In addition, replacing long-chain

saturated fatty acids as triglycerides (diet E) for MCT (diet A and B) had an adverse effect on body weight loss and recovery post-infection.

Acute phase proteins

Fibrinogen, α2-macroglobulin and orosomucoïd are positive acute phase proteins. We observed a strong increase in their concentration after infection. This peaked on day 2 for the two later proteins. For fibrinogen concentrations are two times higher than normal on day 2 and 6.

Albumin is a negative acute phase protein: its concentration is depressed after infection (about half the normal range).

The effects of diets differing in their fatty acid compositions on the recovery of rat following sepsis, suggests that a beneficial outcome can be obtained with diets preferably including the following:

a) MCT as a source of energy
b) Low levels of saturated fatty acids (excluding MCT)
c) α-linolenic acid as a source of n-3 fatty acids rather than the LC-PUFA, EPA, DPA, and DHA derived from fish oil
d) A low n-6/n-3 fatty acid ratio
e) A high lipid content

The beneficial effects of the above defined diets included:

a) Attenuated loss of body weight following infection
b) Better growth rate during the recovery phase (groups A and B)
c) Higher food intake (group A and to a lesser extent group B).

Example 3 - Example of product composition

An example of a composition according to the present invention was prepared. Its composition was as follows:

Nutrient	**% Energy**	**g/L or g/1500Kcal**
Protein	18	67.5
Carbohydrate	37	138.8
Lipid	45	75.0
	%wt of total lipid	**g/L**
MCT	50%	37.5

Saturated (include MCT)	57%	42.8
Monounsaturated	31%	23.3
Polyunsaturated	12%	9.0
Linoleic acid (18:2n-6)	9%	6.8
Alpha-linolenic acid (18:3n-3)	3%	2.3
n-6/n-3 ratio	3.0	

The vitamin and mineral content was at least 25% of the RDA.

The caloric density of the composition was 1.5Kcal/ml.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims.

1. Use of a composition, which comprises at least one lipid wherein the lipid provides greater than 35% total energy of the composition for use in the manufacture of a medicament, functional food or nutritive product for the treatment or prevention of sepsis or inflammatory shock.

2. A method of treatment or prevention of sepsis or inflammatory shock which comprises administering an effective amount of a composition, which comprises at least one lipid wherein the lipid provides greater than 35% total energy of the composition.

3. A method of producing a composition which comprises at least one lipid wherein the lipid provides greater than 35% total energy of the composition, having the steps of blending the constituents, liquefying the blended mixture and homogenising.

4. A composition for use as a medicament, functional food or nutrative product, which comprises at least one lipid wherein the lipid provides greater than 35% total energy of the composition, which further comprises about 25% to about 70% MCT (medium chain triglycerides) by weight of total lipid and less than about 15% by weight saturated fatty acids excluding MCT.

5. A composition according to claim 4, which comprises a n-6/n-3 fatty acid ratio of about 2/1 to 7/1.

6. A composition according to claim 4 or 5, which comprises at least one n-3 fatty acid selected from α-linolenic acid, EPA, DPA or DHA.

7. A composition according to any of claim 4 to 6, which comprises at least one n-6 fatty acid selected from linoleic acid (18:2,n-6), γ-linolenic acid (18:3, n-6), dihomo-γ-linoleinic acid (18:4, n-6) or arachidonic acid (20:4, n-6).

8. A composition according to any of claim 4 to 7 for enteral administration which comprises an acceptable carrier, diluent or adjuvant.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19356 A3

(51) International Patent Classification[7]: A61K 31/23, A23L 1/30, A61P 3/00

(21) International Application Number: PCT/EP00/08731

(22) International Filing Date:
7 September 2000 (07.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99118173.6 13 September 1999 (13.09.1999) EP

(71) Applicant *(for all designated States except US)*: **SOCIETE DES PRODUITS NESTLE S.A.** [CH/CH]; P.O. Box 353, CH-1800 Vevey (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TURINI, Marco** [CH/CH]; 20, chemin du Bois-Murat, CH-1066 Epalinges (CH). **ROESSLE, Claudia** [DE/CH]; 6, chemin de la Brume, CH-1110 Morges (CH). **BREUILLE, Denis** [FR/FR]; 4, route d'Aydat, F-63450 Saint-Saturnin (FR). **CROZIER-WILLI, Gayle** [CA/FR]; Chemin de Confertes, F-74500 Neuvecelle (FR). **FINOT, Paul-André** [FR/CH]; Rte Tirage 1 A, CH-1806 St-Legier (CH). **RICHELLE, Myriam** [BE/CH]; 4, Eden-Roc, Claies-aux-Moines, CH-1073 Savigny (CH). **DUTOT, Guy** [FR/FR]; 11, avenue Georges Buffon, F-78590 Noisy-Le-Roi (FR).

(74) Agent: **LOCK, Graham**; 55, avenue Nestlé, CH-1800 Vevey (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

(88) Date of publication of the international search report:
17 May 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/19356 A3

(54) Title: HIGH LIPID DIET

(57) Abstract: A composition for use as a medicament or nutritional product is described which comprises at least one lipid wherein the lipid provides greater than 35 % total energy of the composition. A prefered embodiment comprises a n-6/n-3 fatty acid ratio of about 2/1 to 7/1. In addition, a method of preparing the composition; use of the composition in the manufacture of a medicament or nutritional product; and a method of treatment or prevention of sepsis or inflammatory shock which comprises administering an effective amount of the composition are described.

Figure 1

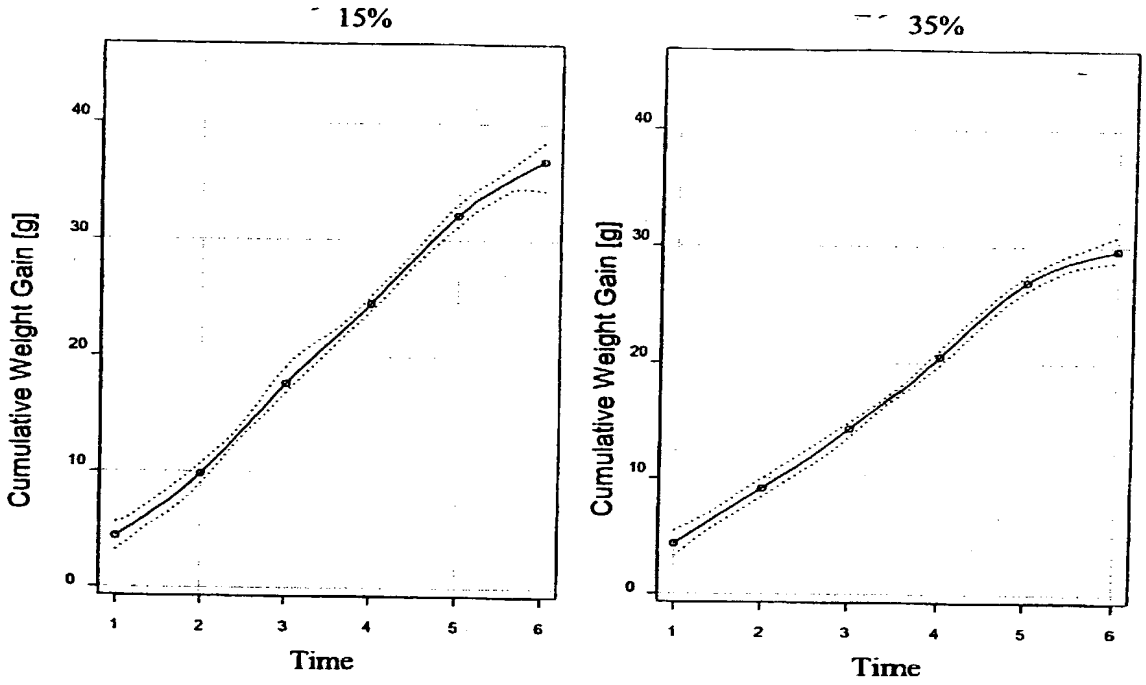


Figure 2

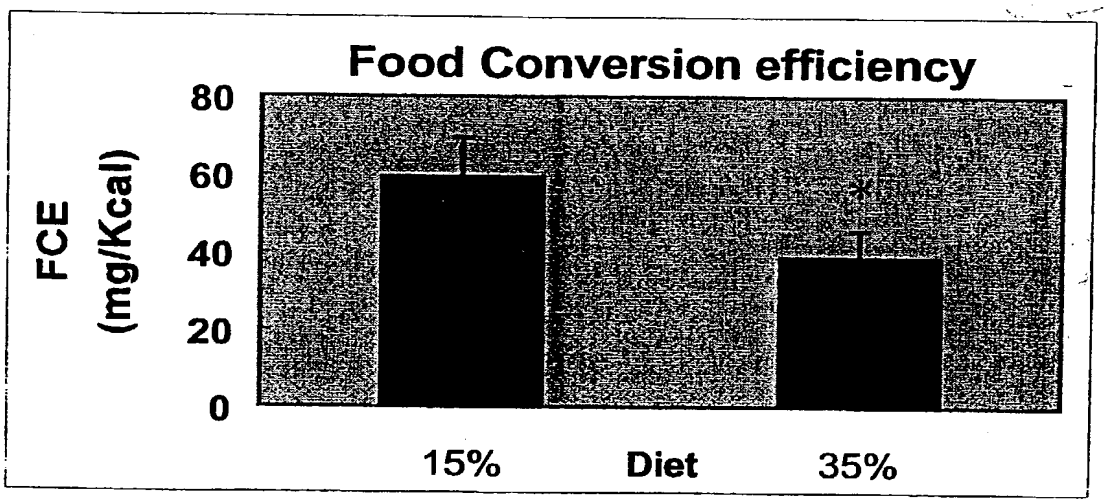

Food Conversion efficiency
FCE (mg/Kcal)
80
60
40
20
0
*
15%
Diet
35%

Figure 3

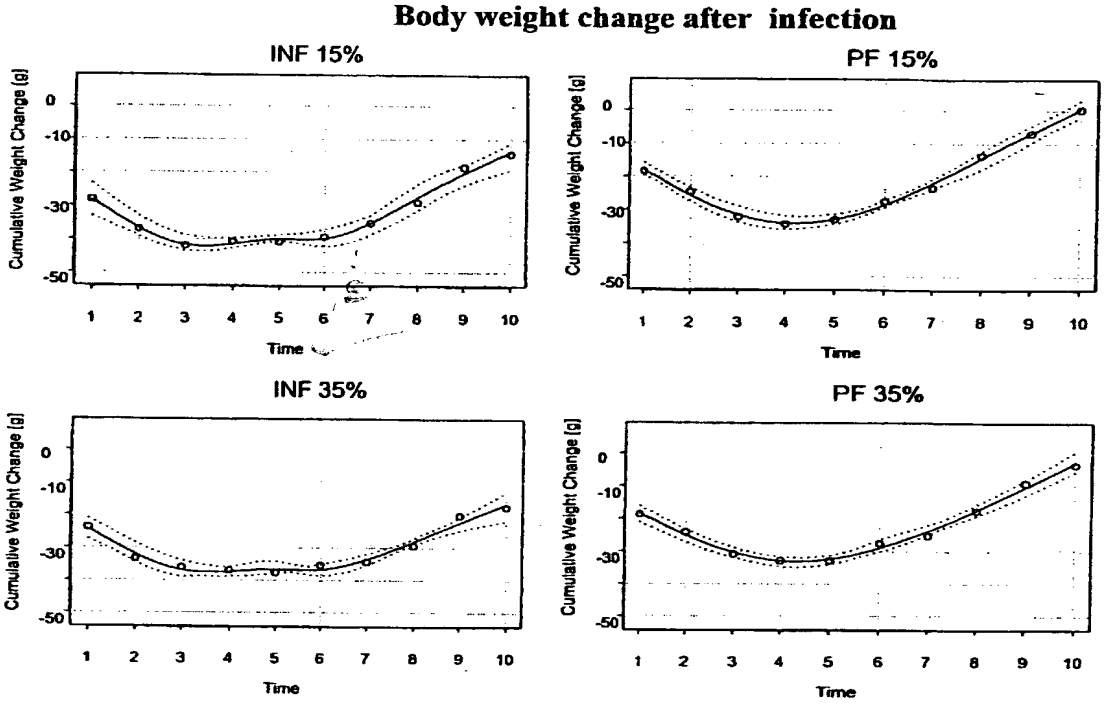

Body weight change after infection
INF 15%
PF 15%
INF 35%
PF 35%
Cumulative Weight Change [g]
0
-10
-30
-50
1 2 3 4 5 6 7 8 9 10
Time

Figure 4

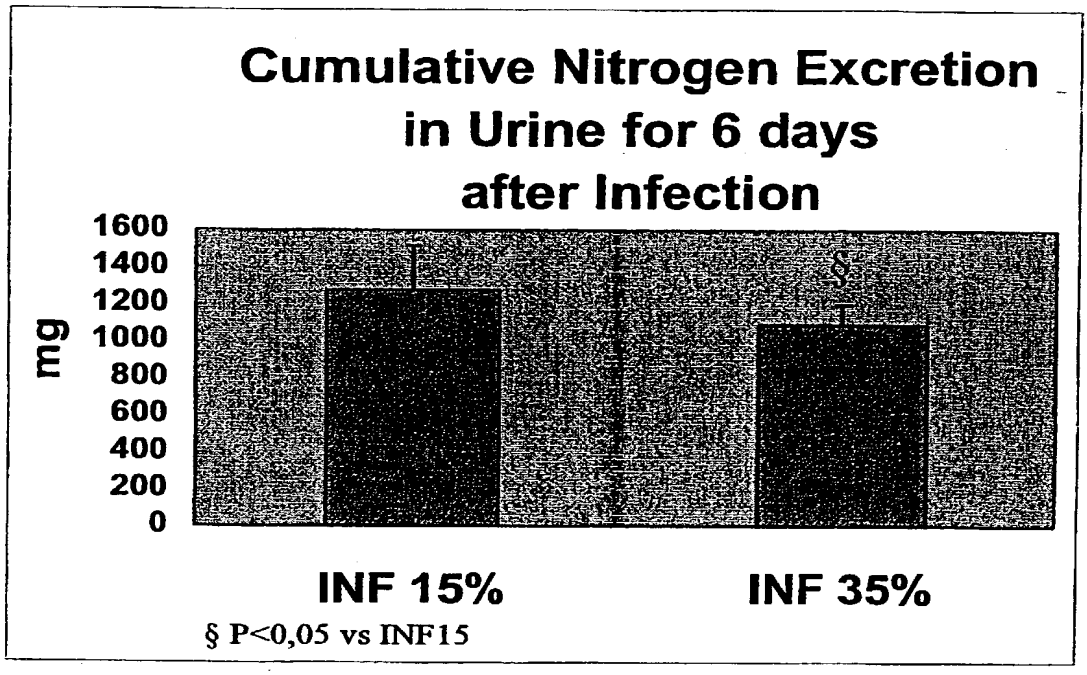

Cumulative Nitrogen Excretion in Urine for 6 days after Infection
mg
1600
1400
1200
1000
800
600
400
200
0
§
INF 15%
INF 35%
§ P<0,05 vs INF15

Figure 5

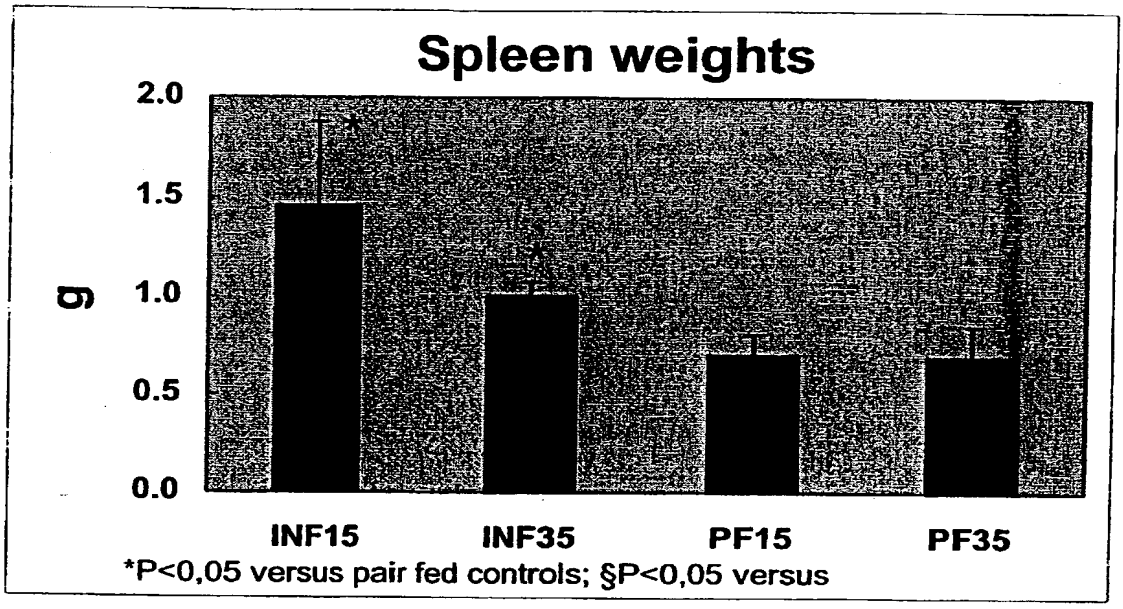

Spleen weights
g
2.0
1.5
1.0
0.5
0.0
INF15
INF35
PF15
PF35
*P<0,05 versus pair fed controls; §P<0,05 versus

Figure 6

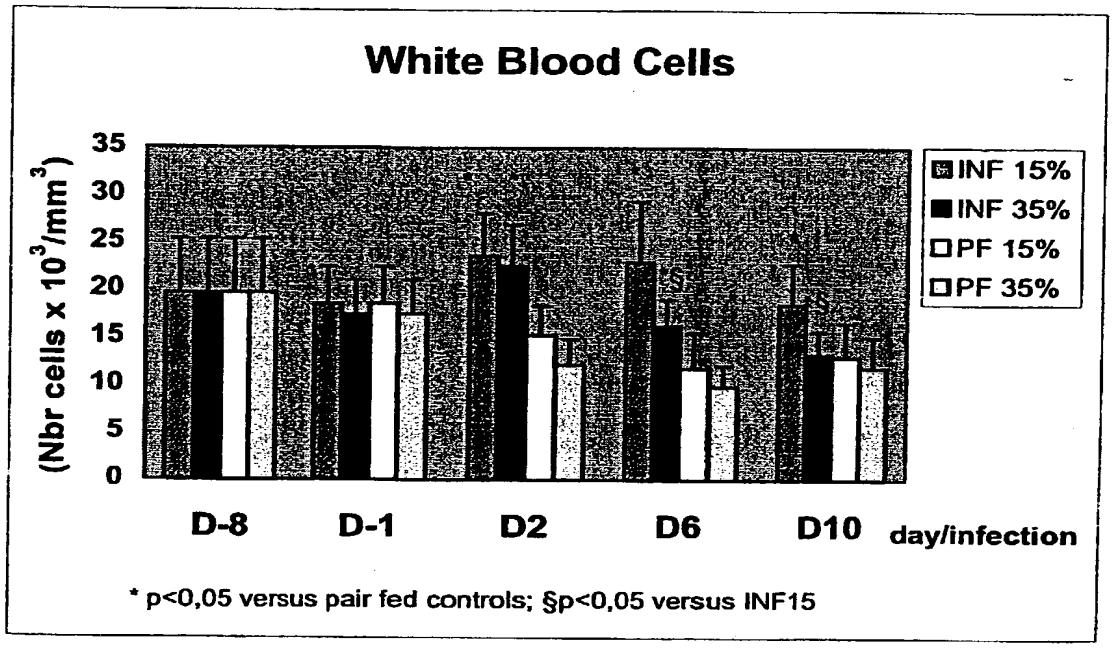

White Blood Cells
(Nbr cells x 10³/mm³)
35
30
25
20
15
10
5
0
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
D10
day/infection
* p<0,05 versus pair fed controls; §p<0,05 versus INF15

Figure 7

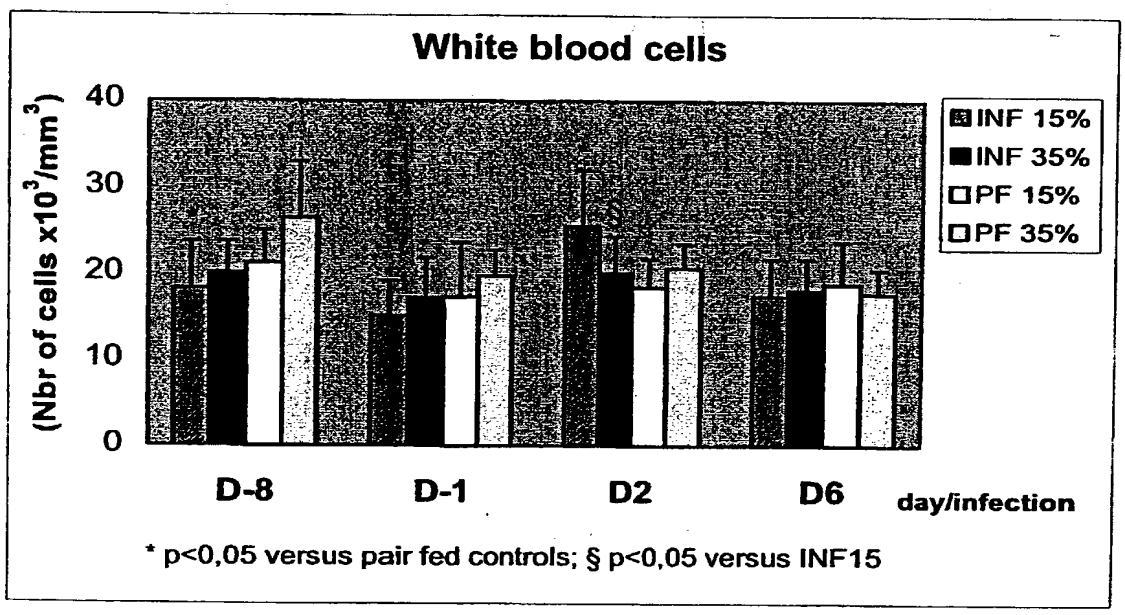

White blood cells
(Nbr of cells x10³/mm³)
40
30
20
10
0
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
day/infection
* p<0,05 versus pair fed controls; § p<0,05 versus INF15

Figure 8

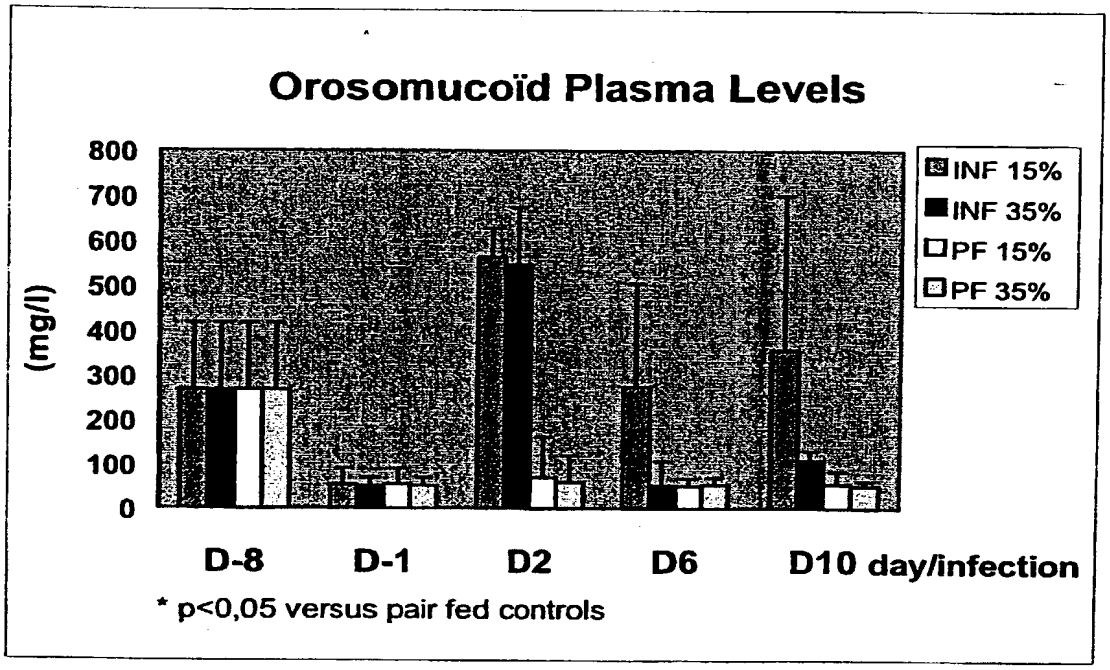

Orosomucoïd Plasma Levels
800
700
600
500
400
300
200
100
0
(mg/l)
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
D10 day/infection
* p<0,05 versus pair fed controls

Figure 9

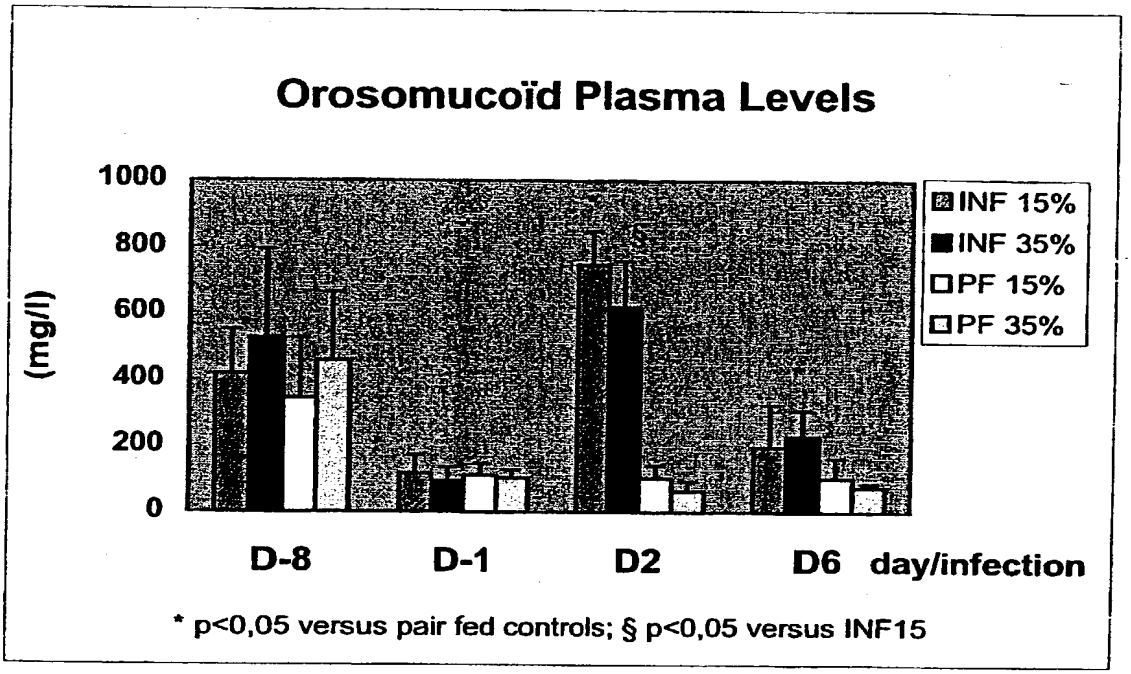

Orosomucoïd Plasma Levels
1000
800
600
400
200
0
(mg/l)
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
day/infection
* p<0,05 versus pair fed controls; § p<0,05 versus INF15

Figure 10

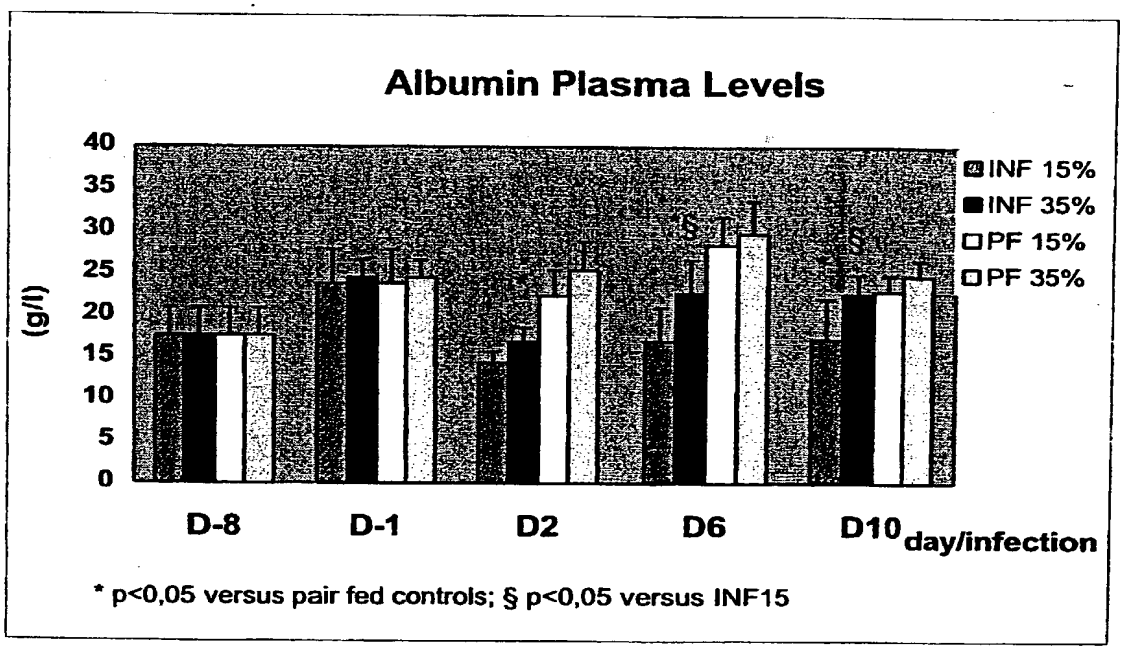

Albumin Plasma Levels
40
35
30
25
20
15
10
5
0
(g/l)
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
D10
day/infection
* p<0,05 versus pair fed controls; § p<0,05 versus INF15

Figure 11

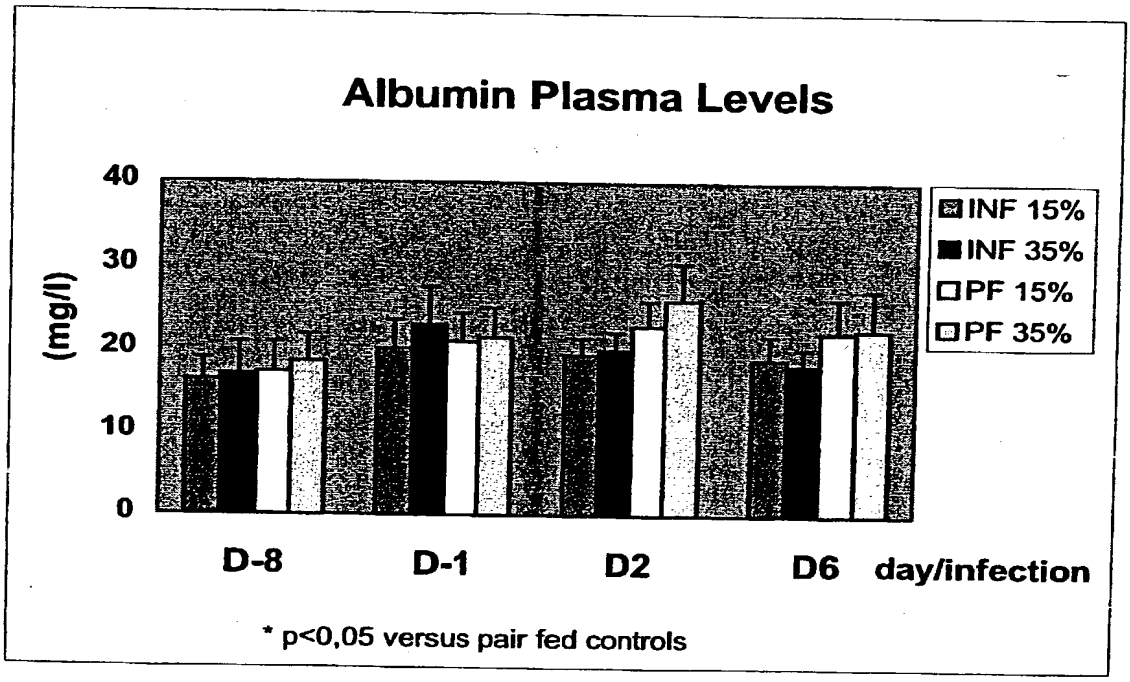

Albumin Plasma Levels
40
30
20
10
0
(mg/l)
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
day/infection
* p<0,05 versus pair fed controls

Figure 12

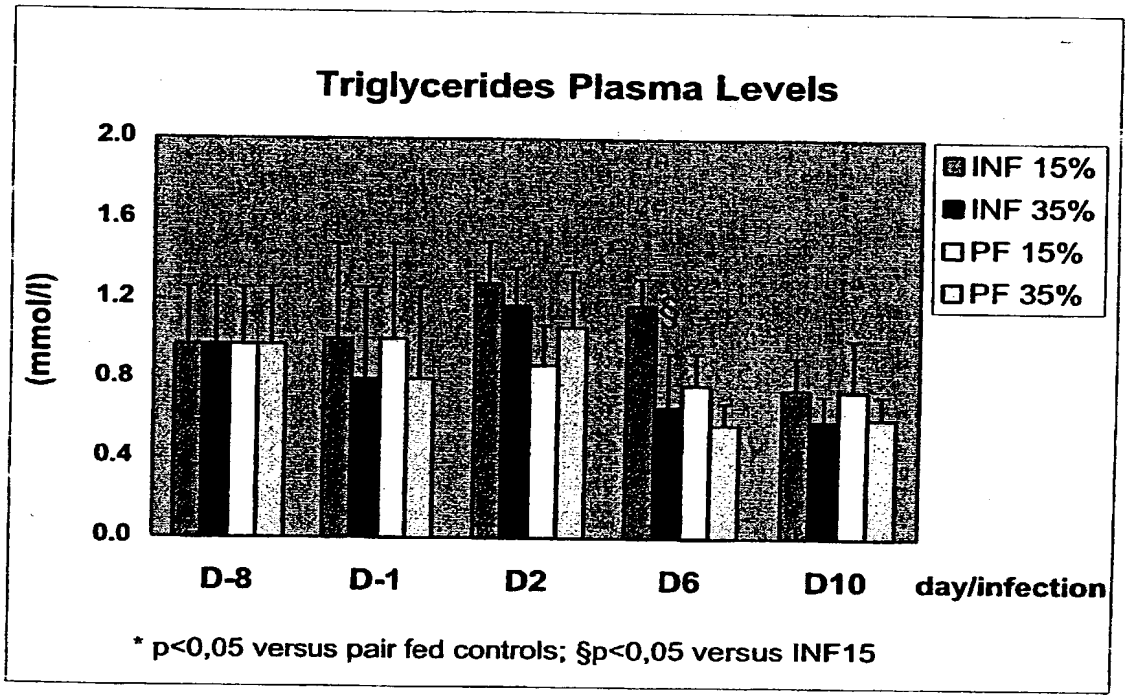
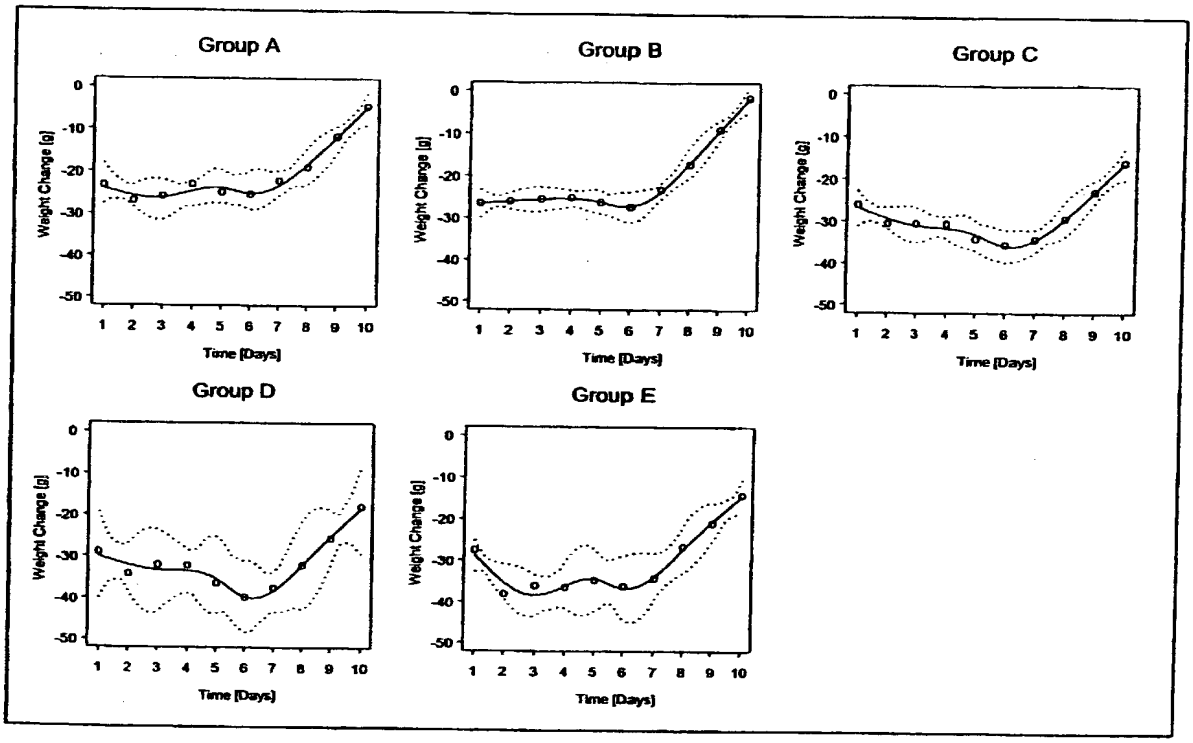

Triglycerides Plasma Levels
2.0
1.6
1.2
0.8
0.4
0.0
(mmol/l)
INF 15%
INF 35%
PF 15%
PF 35%
D-8
D-1
D2
D6
D10
day/infection
* p<0,05 versus pair fed controls; §p<0,05 versus INF15

Figure 13


Group A
Group B
Group C
Group D
Group E
Weight Change [g]
Time [Days]
0
-10
-20
-30
-40
-50
1 2 3 4 5 6 7 8 9 10

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

HIGH LIPID DIET

the specification of which: (check one)

☐ is attached hereto.

☒ was filed on 7 September 2000, as United States Application No. or PCT International Application No. PCT/EP00/08731 and was amended on 6 March 2002 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent Office all information which is known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code Section 119 or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Day/Month/Year Filed	Priority Not Claimed
99118173.6	Europe	13 September 1999	☐
			☐
			☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

Application Serial No.	**Filing Date**

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	**Filing Date**	**Status (patented, pending, abandoned)**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint the practitioners at customer number: 29157

as my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and direct that all correspondence be forwarded to:

Bell, Boyd & Lloyd LLC
P.O. Box 1135
Chicago, Illinois 60690-1135

And all telephone calls be directed to: (312) 807-4204.

1-60	Full name of sole or first inventor **Marco Turini**
	Sole or first inventor's signature M. Turini — Date: 20/06/02
	Residence CH-1066 Epalinges, Switzerland CHX
	Citizenship Switzerland
	Post Office Address 20, chemin du Bois-Murat
	CH-1066 Epalinges, Switzerland

2-60	Full name of second inventor **Claudia Roessle**
	Second inventor's signature Claudia Rössle — Date: 20/06/02
	Residence CH-1110 Morges, Switzerland CHX
	Citizenship Germany
	Post Office Address 6, chemin de la Brume
	CH-1110 Morges, Switzerland

3-60	Full name of third inventor **Denis Breuille**
	Third inventor's signature D Breuille — Date: 21/06/02
	Residence F-63450 Saint-Saturnin, France FRX
	Citizenship France
	Post Office Address 4, route d'Aydat
	F-63450 Saint-Saturnin, France

4th	Full name of fourth inventor **Gayle Crozier-Willi**
	Fourth inventor's signature Gayle Crozier Willi Date 18 July 2002
	Residence F-74500 Neuvecelle, France FRX
	Citizenship Canada
	Post Office Address Chemin de Confertes
	F-74500 Neuvecelle, France

5th	Full name of fifth inventor **Paul André Finot**
	Fifth inventor's signature Paul André Finot Date July 6, 2002
	Residence CH-1806 St-Legier, Switzerland CHX
	Citizenship France
	Post Office Address Rte Tirage 1 A
	CH-1806 St-Legier, Switzerland

6th	Full name of sixth inventor **Myriam Richelle**
	Sixth inventor's signature Date 1.7.02
	Residence CH-1073 Savigny, Switzerland CHX
	Citizenship Belgium
	Post Office Address 4, Eden-Roc, Claies-aux-Moines
	CH-1073 Savigny, Switzerland

Full name of seventh inventor **Guy Dutot**
Seventh inventor's signature Date July 4th, 200
Residence F-78590 Noisy-Le-Roi, France
Citizenship France
Post Office Address 11, avenue Georges Buffon
F-78590 Noisy-Le-Roi, France

Full name of eighth inventor
Eighth inventor's signature Date
Residence
Citizenship
Post Office Address

Full name of ninth inventor
Ninth inventor's signature Date
Residence
Citizenship
Post Office Address